Adjusting for Covariates in Randomized Clinical Trials with Continuous Outcomes

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Draft guidance on covariate adjustment

- The draft guidance was released last April:
  - https://www.fda.gov/media/123801/download

- Scope of the guidance:
  - Randomized clinical trials
  - Continuous endpoints
  - Linear models

- The draft guidance has five bulleted recommendations

Recommendation #1

- *"Sponsors can use ANCOVA to adjust for differences between treatment groups in relevant baseline variables to improve the power of significance tests and the precision of estimates of treatment effect."*

Comments on Recommendation #1

- Covariate adjustment appears to be underutilized in clinical trials
- The draft guidance endorses covariate adjustment
- The goal of adjustment should be to improve precision

Recommendation #2

- *"Sponsors should not use ANCOVA to adjust for variables that might be affected by treatment."*

Comments on Recommendation #2

- Including post-randomization variables in the adjustment model could introduce confounding
  - For instance, the treatment effect on an outcome score at Week 8 would be biased if conditioning on patients with high scores at Week 6

- The recommendation pertains to the primary analysis, and does not cover the handling of post-randomization data for imputing missing outcomes or for sensitivity analyses

Recommendation #2 continued

- *"Even when the ANCOVA model does not closely approximate the true relationship between the outcome and the covariates, the probability of type I error is still maintained at the nominal level, and therefore misspecification of the relationship between the outcome and the covariates will not invalidate the results."*

Comments on Recommendation #2

- Covariate adjustment for the average treatment effect remains valid even without the usual full suite of textbook linear model assumptions:
  - Correctness of linear functional form, Gaussian distributed errors, constant error variance, etc.

- The draft guidance does not cover the technical fine print that this performance guarantee depends on using robust standard error estimation:
  - Lin W. Agnostic notes on regression adjustments to experimental data: Reexamining Freedman's critique. Annals of Applied Statistics 2013;7(1):295-318.

Simulations on Recommendation #2

- Let X represent a continuous baseline covariate that is normally distributed with mean 50 and SD 10.
- Let ε represent an error term that is normally distributed with mean 0 and SD 20.
- For each of 10,000 iterations do the following (each iteration mimicking an RCT):

  -- randomly set T=1 for 1000 pretend experimental treatment participants and set T=0 for 1000 pretend control participants.

  -- randomly assign X and ε values to the 2000 participants.

  -- set each participant's Y value according to the equation

$$Y = 100 + 25T + .5X^2 + \varepsilon$$

Simulations on Recommendation #2

- Using the simulated data set just created, estimate each of the following four linear regression equations via SAS

$$Y = \beta_0 + \beta_1 T + \varepsilon_\beta$$

$$Y = \alpha_0 + \alpha_1 T + \alpha_2 X + \varepsilon_\alpha$$

$$Y = \gamma_0 + \gamma_1 T + \gamma_2 \sqrt{X} + \varepsilon_\gamma$$

$$Y = \pi_0 + \pi_1 T + \pi_2 X^2 + \varepsilon_\pi$$

Simulations on Recommendation #2

- Averaging over the 10,000 iterations (i.e., over 10,000 pretend RCTs):

  -- mean $\widehat{\beta_1} = 25.065$

  -- mean $\widehat{\alpha_1} = 25.014$

  -- mean $\hat{\gamma}_1 = 25.014$

  -- mean $\widehat{\pi_1} = 25.005$

Recommendation #3

- *"The sponsor should prospectively specify the covariates and the mathematical form of the model in the protocol or statistical analysis plan. When these specifications are unambiguous, FDA will not generally be concerned about the sensitivity of results to the choice of covariates because differences between adjusted estimators and unadjusted estimators of the same parameter, or between adjusted estimators using different models, are random."*

Comments on Recommendation #3

- Consistency between adjusted and unadjusted estimators is not required
- Imbalances observed post-hoc may be analyzed but the emphasis will be on the prespecified analysis, which can be either adjusted or unadjusted
- Prespecifying adjustment for important covariates helps prevent interpretational difficulties due to random imbalances

Comments on Recommendation #3

- Prespecification of variables does not cover only prespecifying the variable selection process, such as forwards or backwards selection
- Adaptive choice of covariates is beyond the scope of the guidance and should be discussed with FDA
- The draft guidance does not provide specific recommendations on the number of covariates to include in the adjustment model
- The precision gain from covariate adjustment depends on the strength of association between covariates and the outcome

Recommendation #4

- *"Interaction of the treatment with covariates is important, but the presence of an interaction does not invalidate ANCOVA as a method of estimating and testing for an overall treatment effect, even if the interaction is not accounted for in the model."*

Comments on Recommendation #4

- It is important to clearly distinguish what question is being asked versus what method is being used

- Primary analysis question: What is the average treatment effect?
  - Covariate adjusted estimation of the overall treatment effect can be valid with or without interaction terms in a linear model

- Secondary or exploratory analysis question: how does the treatment effect differ for patients with different covariates?
  - Modeling would need to include interaction terms
  - Clinical trials are usually underpowered for this question

Recommendation #5

- *"Even when the outcome is measured as a change from baseline, the baseline value can still be used advantageously as a covariate."*

Comments on Recommendation #5

- It is usually advantageous to adjust for the baseline value

- For estimating the (unconditional) average treatment effect, redefining the outcome as a change from baseline does not alter the estimand

What is not covered in the guidance?

- Nonlinear models
- Outcomes not measured on a continuous scale
- Repeated measures or longitudinal data
- Missing covariate data
- Handling of stratification variables in the analysis
- The number of covariates to include in the model
- Technical details of implementation

- The draft guidance should not be read as an endorsement of unadjusted estimation for cases that are not explicitly covered

Summary

- The draft guidance endorses covariate adjustment
- Covariate adjustment provides valid estimation of average treatment effects under minimal assumptions, and can often improve precision
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